Arch Chemicals, Inc.
501 Merritt 7
P. O. Box 5204
Norwalk, CT 06856-5204
Tel 203.229.2900

8EHQ-1001-15018

5255H

TS7407 Document Control Officer
TSCA Data Processing Center
G99 East Tower, Waterside Mall
USEPA
401 M Street, SW
Washington, DC 20460

Contain NO CBI

RE: TSCA 8(e): Zinc Pyrithione
(CAS# 13463-41-7; EPA Chemical Code 088002)
Preliminary Results Following Dermal Application.

Dear Sir/Madam:

Arch Chemicals, Inc. is in the process of evaluating zinc pyrithione in an Absorption, Distribution and Excretion (ADE) study. Based on the preliminary data from this testing the following information is being submitted for your review under the provisions and specifications of TSCA 8(e). The compilation of data from the ADE study is not complete and the information that follows is raw data and is the only data available at this time. On September 25th, 2001 Arch Chemicals, Inc. became aware of unaudited draft data from the pilot study for electrophysiology and functional endpoints portion of the ADE study being carried out in Sprague -Dawley rats exposed to zinc pyrithione (ZPT) that produced new information following dermal application. Testing began in satellite groups of animals exposed to ZPT in the diet at 50 and 250 ppm and with one group of rats being exposed to 100 mg/kg via dermal application. Neurological effects observed in the rat, e.g., hindlimb weakness, are widely known to result from oral administration of ZPT, but was not previously observed from dermal application at this dose level. These results are not considered a substantial risk but do constitute new information following dermal application of 100 mg/kg in the rat.

The new information from the pilot study following dermal application, not previously observed for ZPT, are summarized below:

Arch Chemicals, Inc.
501 Merritt 7
P. O. Box 5204
Norwalk, CT 06856-5204
Tel 203.229.2900

Pilot Study via Dermal Exposure:

The pilot study was designed to evaluate the effects of dermal application of ZPT on the evoked compound muscle action potential (CMAP), as measured from the extensor muscle of the tarsus after stimulation of the sciatic nerve. A decrement in the amplitude of the muscle potential has been shown previously to provide a sensitive correlate for the observed muscle weakness (reversible) resulting from 7-days of consecutive oral exposure to ZPT to the rat in the diet. Previously, studies conducted by Arch Chemicals, Inc., MRID Number 42827902, following dermal application of 10, 100, or 1000 mg/kg 5-days/week for 13 weeks failed to produce any signs of hindlimb weakness at any level of exposure. The purpose of this ADE study is to compare the kinetics of ZPT disposition in exposed orally (observed route to cause reversible hindlimb weakness in the rat) and dermally (not previously observed to produce hindlimb weakness). By defining the kinetics for the development of subtle changes in the electrophysiology, that precedes the clinical observation of hindlimb weakness by 2-3 days, we hope to increase the confidence of the risk assessments for ZPT uses and applications.

Results:

In the pilot study all animals exhibited at least some decrement in the CMAP amplitude, with 4 out of 5 animals showing evidence of reduced muscle tone (extensor response, hindlimb weakness) following 10-consecutive days of exposure to ZPT at 100 mg/kg via dermal application.

The fact that a decrement in the CMAP amplitude in conjunction with reduced muscle tone (hindlimb weakness) was observed in the animals dosed at 100 mg/kg dermally for 10-consecutive days constitutes new information that had not been previously observed following dermal application. Again, as previously stated, an earlier dermal study conducted in the same strain of rat failed to show any effects on the hindlimb clinically or pathologically. The main difference between the 2 studies is that in the earlier study the animals were dosed 5-days a week for 13-weeks and in this study the animals were dosed for 10-concsecutive days. Previous reports noted that treating animals orally for 5-days a week with no dosing over the weekend followed by dosing beginning again on Monday delayed the onset of hindlimb effects (in most cases being delayed 1-2 weeks).

Arch Chemicals, Inc.
501 Merritt 7
P. O. Box 5204
Norwalk, CT 06856-5204
Tel 203.229.2900

Discussion:

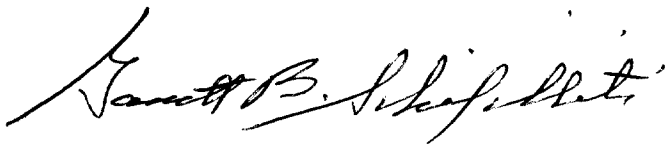
Arch Chemicals does not consider this new information as a substantial risk especially in light of previous risk assessments carried out by OPPTS scientific staff which incorporated values for dermal penetration of ZPT at 3-6% where these data suggest a value in the range of 2-3% for dermal penetration.

A repeat study of dermal application with 100 mg/kg of ZPT to rats was done to verify these results. Late Monday (October 8th, 2001) Arch Chemical, Inc. received verbal notice that the dermal application of 100 mg/kg for 10-consecutive days resulted in 3 out of 5 animals being observed with a decrement in the CMAP amplitude in conjunction with reduced muscle tone (hindlimb weakness), thus confirming this effect via dermal exposure.

The finding of hindlimb weakness in the rat following dermal application is new information and not previously observed for this route of administration. The ADE study is proceeding and we will be forwarding the final report upon completion.

If you have any question or require additional information please contact me.

Sincerely,



Garrett B. Schifilliti
Manager, Regulatory Services
(203) 229-3510
(203) 229-2709 Fax
gbschifilliti@archchemicals.com